For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

EVERBLISS
(Everolimus Tablets)

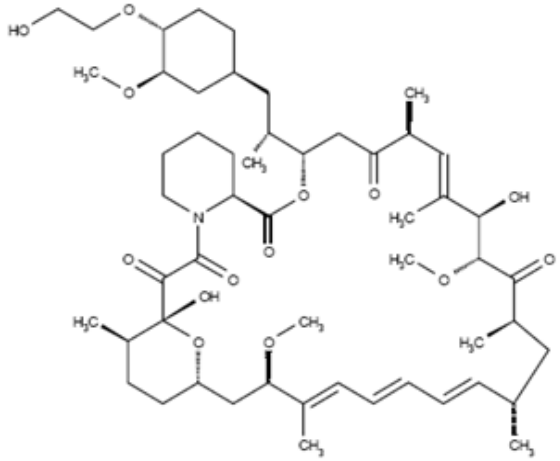
COMPOSITION

EVERBLISS 5
Each Tablet contains:
Everolimus 5mg
Excipients q.s.

EVERBLISS 10
Each Tablet contains:
Everolimus 10mg
Excipients q.s.

DESCRIPTION

Everolimus, an inhibitor of mammalian target of rapamycin (mTOR), is an antineoplastic agent. The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E, 30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclo hexyl]-1-methylethyl}-19,30-dimethoxy15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20pentaone. The molecular formula is $C_{53}H_{83}NO_{14}$ and the molecular weight is 958.2. The structural formula is:



CLINICAL PHARMACOLOGY

Mechanism of Action

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP1), downstream effectors of mTOR, involved in protein synthesis. S6K1 is a substrate of mTORC1 and phosphorylates the activation domain 1 of

the estrogen receptor which results in ligand-independent activation of the receptor. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies.

Constitutive activation of the PI3K/Akt/mTOR pathway can contribute to endocrine resistance in breast cancer. In vitro studies show that estrogen-dependent and HER2+ breast cancer cells are sensitive to the inhibitory effects of everolimus, and that combination treatment with everolimus and Akt, HER2, or aromatase inhibitors enhances the anti-tumor activity of everolimus in a synergistic manner.

Two regulators of mTORC1 signaling are the oncogene suppressors tuberin-sclerosis complexes 1 and 2 (TSC1, TSC2). Loss or inactivation of either TSC1 or TSC2 leads to activation of downstream signaling. In TSC, a genetic disorder, inactivating mutations in either the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body.

PHARMACODYNAMICS

Exposure Response Relationships

Markers of protein synthesis show that inhibition of mTOR is complete after a 10 mg daily dose. However, as responses have been observed at trough concentrations as low as 5 ng/mL, once acceptable efficacy has been achieved, additional dose increase may not be necessary.

PHARMACOKINETICS

Absorption

After administration of Everolimus tablets in patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to 70 mg. Following single doses, C_{max} is dose-proportional with daily dosing between 5 mg and 10 mg. With single doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within 2 weeks following once-daily dosing.

Food effect: In healthy subjects, high-fat meals reduced systemic exposure to Everolimus 10 mg tablet (as measured by AUC) by 22% and the peak blood concentration Cmax by 54%. Light-fat meals reduced AUC by 32% and C_{max} by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given everolimus 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Metabolism
Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself.

In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan.

Elimination
No specific elimination studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabeled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

Patients with Renal Impairment
Approximately 5% of total radioactivity was excreted in the urine following a 3 mg dose of [^{14}C]-labeled everolimus. In a population pharmacokinetic analysis which included 170 patients with advanced cancer, no significant influence of creatinine clearance (25–178 mL/min) was detected on oral clearance (CL/F) of everolimus.
Patients with Hepatic Impairment

The safety, tolerability and pharmacokinetics of everolimus were evaluated in a single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects (N=13), there was a 1.8-fold, 3.2-fold, and 3.6-fold increase in exposure (i.e. AUC) for subjects with mild (Child-Pugh class A, n=6), moderate (Child-Pugh class B, n=9), and severe (Child-Pugh class C, n=6) hepatic impairment, respectively. In another study, the average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function.

For advanced Renal Cell Ccarcinoma with severe hepatic impairment, everolimus may be used at a reduced dose if the desired benefit outweighs the risk. For patients with moderate or mild hepatic impairment, a dose reduction is recommended.

Effects of Age and Gender
In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender.

Ethnicity
Based on a cross-study comparison, Japanese patients (n=6) had on average exposures that were higher than non-Japanese patients receiving the same dose.

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in black patients than in Caucasians.

The significance of these differences on the safety and efficacy of everolimus in Japanese or black patients has not been established.

QT/QTc Prolongation Potential
In a randomized, placebo-controlled, cross-over study, 59 healthy subjects were administered a single oral dose of everolimus (20 mg and 50 mg) and placebo. There is no indication of a QT/QTc prolonging effect of Everolimus in single doses up to 50 mg.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding respectively to 3.9 and 0.2 times the estimated clinical exposure (AUC_{0-24h}) at the 10 mg daily human dose.

Everolimus was not genotoxic in a battery of in vitro assays (Ames mutation test in Salmonella, mutation test in L5178Y mouse lymphoma cells, and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not genotoxic in an in vivo mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m2/day, approximately 255fold the 10 mg daily human dose, and 103-fold the maximum dose administered to patients with SEGA, based on the body surface area), administered as 2 doses, 24 hours apart.

Based on non-clinical findings, male fertility may be compromised by treatment with Everolimus. In a 13-week male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above. Sperm motility, sperm count, and plasma testosterone levels were diminished in rats treated with 5 mg/kg. These doses result in exposures which are within the range of therapeutic exposure (52 ng•hr/mL and 414 ng•hr/mL respectively compared to 560 ng•hr/mL human exposure at 10 mg/day), and resulted in infertility in the rats at 5 mg/kg. Effects on male fertility occurred at the AUC_{0-24h} values below that of therapeutic exposure (approximately 10%-81% of the AUC_{0-24h} in patients receiving the 10 mg daily dose). After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 60% (12/20 mated females were pregnant).

Oral doses of everolimus in female rats at $\geq$0.1 mg/kg (approximately 4% the AUC_{0-24h} in patients receiving the 10 mg daily dose) resulted in increased incidence of pre-implantation loss, suggesting that the drug may reduce female fertility.

Animal Toxicology and/or Pharmacology
In juvenile rat toxicity studies, dose-related delayed attainment of developmental landmarks including delayed eye-opening, delayed reproductive development in males and females and increased latency time during the learning and memory phases were observed at doses as low as 0.15 mg/kg/day.

INDICATION

Everolimus is indicated for the treatment of advance renal cell carcinoma

DOSE AND METHOD OF ADMINISTRATION

The recommended dose of Everolimus Tablets are 5mg and 10mg, to be taken once daily at the same time every day. Administer either consistently with food or consistently without food. Everolimus Tablets should be swallowed whole with a glass of water. Do not break or crush tablets.

Continue treatment until disease progression or unacceptable toxicity occurs.

Dose Modifications in renal cell carcinoma: Management of severe or intolerable adverse reactions may require temporary dose interruption (with or without a dose reduction of Everolimus therapy) or discontinuation. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered.

Recommendations for dose reduction, interruption or discontinuation of Everolimus in the management of adverse reactions. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Hepatic Impairment

Hepatic impairment will increase the exposure to everolimus. Dose adjustments are recommended:

- Mild hepatic impairment (Child-Pugh class A) – The recommended dose is 7.5 mg daily; the dose may be decreased to 5 mg if not well tolerated.
- Moderate hepatic impairment (Child-Pugh class B) – The recommended dose is 5 mg daily; the dose may be decreased to 2.5 mg if not well tolerated.
- Severe hepatic impairment (Child-Pugh class C) – If the desired benefit outweighs the risk, a dose of 2.5 mg daily may be used but must not be exceeded.

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

CYP3A4/P-glycoprotein (PgP) Inhibitors

Avoid the use of strong CYP3A4/PgP inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole).

Use caution when co-administered with moderate CYP3A4/PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem). If patients require co-administration of a moderate CYP3A4 /PgP inhibitor, reduce the Everolimus dose to 2.5 mg daily. The reduced dose of Everolimus is predicted to adjust the area under the curve (AUC) to the range observed without inhibitors. An Everolimus dose increase from 2.5 mg to 5 mg may be considered based on patient tolerance. If the moderate inhibitor is discontinued, a washout period of approximately 2 to 3 days should be allowed before the Everolimus dose is increased. If the

moderate inhibitor is discontinued, the Everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor.

Grapefruit, grapefruit juice, and other foods that are known to inhibit cytochrome P450 and PgP activity may increase everolimus exposures and should be avoided during treatment.

Strong CYP3A4/PgP Inducers
Avoid the use of concomitant strong CYP3A4/PgP inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). If patients require co-administration of a strong CYP3A4/PgP inducer, consider doubling the daily dose of Everolimus using increments of 5 mg or less. This dose of Everolimus is predicted, based on pharmacokinetic data, to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4/PgP inducers. If the strong inducer is discontinued, consider a washout period of 3 to 5 days, before the everolimus dose is returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

St. John's Wort (Hypericum perforatum) may decrease everolimus exposure unpredictably and should be avoided.

CONTRAINDICATIONS
Everolimus is contraindicated in patients with hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

WARNINGS AND PRECAUTIONS
Non-infectious Pneumonitis
Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Everolimus. Non-infectious pneumonitis was reported in up to 19% of patients treated with Everolimus in clinical trials. The incidence of Common Terminology Criteria (CTC) Grade 3 and 4 non-infectious pneumonitis was up to 4.0% and up to 0.2%, respectively. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Opportunistic infections such as pneumocystis jiroveci pneumonia (PJP) should be considered in the differential diagnosis. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Everolimus therapy without dose alteration. Imaging appears to overestimate the incidence of clinical pneumonitis.

If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases of Grade 3 non-infectious pneumonitis interrupt Everolimus until resolution to less than or equal to Grade 1. Everolimus may be re-introduced at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances. If toxicity recurs at Grade 3, consider discontinuation of Everolimus. For cases of Grade 4 non-infectious pneumonitis, discontinue Everolimus. Corticosteroids may be indicated until clinical symptoms resolve. For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for PJP may be considered. The development of pneumonitis has been reported even at a reduced dose.

Infections
Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections, such as aspergillosis, candidiasis, or pneumocystis jiroveci pneumonia (PJP) and viral infections including reactivation of hepatitis B virus have occurred in patients taking Everolimus. Some of these infections have been severe (e.g., leading to sepsis, respiratory or hepatic failure) or fatal. Physicians and patients should be aware of the increased risk of infection with Everolimus. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with Everolimus. While taking Everolimus, be vigilant for signs and symptoms of infection; if a diagnosis of an infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Everolimus. If a diagnosis of invasive systemic fungal infection is made, discontinue Everolimus and treat with appropriate antifungal therapy. Pneumocystis jiroveci pneumonia, some with a fatal outcome, has been reported in patients who received everolimus. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

Oral Ulceration
Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with Everolimus at an incidence ranging from 44%-78% across the clinical trial experience. Grade 3 or 4 stomatitis was reported in 4%-9% of patients. In such cases, topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme- containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed.

Renal Failure
Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Everolimus.

Impaired Wound Healing
Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma. These

wound-related complications may require surgical intervention. Exercise caution with the use of Everolimus in the peri-surgical period.

Geriatric Patients
In the randomized advanced hormone receptor-positive, HER2-negative breast cancer study, the incidence of deaths due to any cause within 28 days of the last Everolimus dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended.

Laboratory Tests and Monitoring
Renal Function
Elevations of serum creatinine and proteinuria have been reported in patients taking Everolimus. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of Everolimus therapy and periodically thereafter. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function.

Blood Glucose and Lipids
Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in patients taking Everolimus. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of Everolimus therapy and periodically thereafter as well as management with appropriate medical therapy. More frequent monitoring is recommended when Everolimus is co-administered with other drugs that may induce hyperglycemia. When possible, optimal glucose and lipid control should be achieved before starting a patient on Everolimus.

Hematologic Parameters
Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in patients taking Everolimus . Monitoring of complete blood count is recommended prior to the start of Everolimus therapy and periodically thereafter.

Drug-drug Interactions
Due to significant increases in exposure of everolimus, co-administration with strong CYP3A4/PgP inhibitors should be avoided. A reduction of the everolimus dose is recommended when co-administered with a moderate CYP3A4/PgP inhibitor. An increase in the everolimus dose is recommended when co-administered with a strong CYP3A4/PgP inducer.

Hepatic Impairment
Exposure to everolimus was increased in patients with hepatic impairment. For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment (Child-Pugh class C), everolimus may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended. For patients with SEGA and mild or moderate hepatic impairment, adjust the dose of everolimus Tablet based on therapeutic drug monitoring. For patients with SEGA and severe hepatic impairment, reduce the

starting dose of everolimus Tablets approximately 50% and adjust subsequent doses based on therapeutic drug monitoring.

Vaccinations
During Everolimus treatment, avoid the use of live vaccines and avoid close contact with individuals who have received live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

Embryo-fetal Toxicity
Based on the mechanism of action, everolimus can cause fetal harm. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Advise female patients of reproductive potential to avoid becoming pregnant and to use highly effective contraception while using everolimus and for up to 8 weeks after ending treatment.

DRUG INTERACTIONS
Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Agents That May Increase Everolimus Blood Concentrations
CYP3A4 Inhibitors and PgP Inhibitors
In healthy subjects, compared to Everolimus treatment alone there were significant increases in everolimus exposure when Everolimus was coadministered with:

- Ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 3.9- and 15.0-fold, respectively.
- Erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.0- and 4.4-fold, respectively.
- Verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong inhibitors of CYP3A4/PgP should not be used.

Use caution when Everolimus is used in combination with moderate CYP3A4/PgP inhibitors. If alternative treatment cannot be administered reduce the Everolimus dose.

Agents That May Decrease Everolimus Blood Concentrations
CYP3A4/PgP Inducers
In healthy subjects, co-administration of everolimus with rifampin, a strong inducer of CYP3A4 and an inducer of PgP, decreased everolimus AUC and Cmax by 63% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of everolimus when co-administered with strong CYP3A4/PgP inducers if alternative treatment cannot be administered. St. John’s Wort may decrease everolimus exposure unpredictably and should be avoided.

Drugs That May Have Their Plasma Concentrations Altered by Everolimus
Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between everolimus and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of everolimus.
A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam (sensitive CYP3A4 substrate) with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0\text{-}inf)}$.

Coadministration of everolimus and exemestane increased exemestane C_{min} by 45% and C2h by 64%. However, the corresponding estradiol levels at steady state (4 weeks) were not different between the 2 treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination.

Co-administration of everolimus and depot octreotide increased octreotide Cmin by approximately 50%.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category D
Risk Summary
Based on the mechanism of action, Everolimus can cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, apprise the patient of the potential hazard to the fetus.

Animal Data
In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities in rats occurred at doses ≥0.1 mg/kg (0.6 mg/m2) with resulting exposures of approximately 4% of the exposure ($AUC_{0\text{-}24h}$) achieved in patients receiving the 10 mg daily dose of everolimus. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose of 0.8 mg/kg (9.6 mg/m^2), approximately 1.6 times either the 10 mg daily dose or the median dose administered to SEGA patients on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At the dose of 0.1 mg/kg (0.6 mg/m^2), there were no adverse effects on delivery and lactation or signs of maternal toxicity; however, there were reductions in body weight (up to 9% reduction from the control) and in survival of offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

Nursing Mothers
It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use
In two other randomized trials (advanced renal cell carcinoma and advanced neuroendocrine tumors of pancreatic origin), no overall differences in safety or effectiveness were observed between elderly and younger patients. In the randomized advanced RCC study, 41% of Everolimus treated patients were ≥ 65 years of age, while 7% were 75 years and over. In the randomized advanced PNET study, 30% of Everolimus -treated patients were ≥ 65 years of age, while 7% were 75 years and over.

Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

No dosage adjustment in initial dosing is required in elderly patients, but close monitoring and appropriate dose adjustments for adverse reactions is recommended.

Females and Males of Reproductive Potential
Contraception
Females
Everolimus can cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use highly effective contraception while receiving Everolimus and for up to 8 weeks after ending treatment.

Infertility
Females
Menstrual irregularities, secondary amenorrhea, and increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH) occurred in female patients taking Everolimus. Based on these clinical findings and findings in animals, female fertility may be compromised by treatment with Everolimus.

Males
Everolimus treatment may impair fertility in male patients based on animal findings.

Renal Impairment
No clinical studies were conducted with Everolimus in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment.

Hepatic Impairment

The safety, tolerability and pharmacokinetics of Everolimus were evaluated in a 34 subject single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Exposure was increased in patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment.

For advanced HR+ BC, advanced PNET, advanced Renal Cell Carcinoma, and renal angiomyolipoma with TSC patients with severe hepatic impairment, Everolimus may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended.

For patients with SEGA who have severe hepatic impairment (Child-Pugh class C), reduce the starting dose of Everolimus Tablets by approximately 50%. For patients with SEGA who have mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, adjustment to the starting dose may not be needed. Subsequent dosing should be based on therapeutic drug monitoring.

ADVERSE REACTIONS

- Non-infectious pneumonitis
- Infections
- Oral ulceration
- Renal failure
- Impaired wound healing

Clinical Study Experience in Advanced Renal Cell Carcinoma

The data described below reflect exposure to Everolimus (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451 days) for patients receiving Everolimus and 60 days (range 21-295 days) for those receiving placebo.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common Grade 3-4 adverse reactions (incidence ≥ 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common Grade 3-4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the Everolimus arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the Everolimus and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment

delay or dose reduction. The most common medical interventions required during Everolimus treatment were for infections, anemia, and stomatitis.

Table compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10% for patients receiving Everolimus 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Adverse Reactions Reported in at Least 10% of Patients with Renal Cell Carcinoma and at a Higher Rate in the Everolimus Arm than in the Placebo Arm

	Everolimus 10 mg/ day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	97	52	13	93	23	5
Gastrointestinal disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and infestations[b]	37	7	3	18	1	0
General disorders and administration site conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis[c]	14	4	0	0	0	0
Skin and subcutaneous tissue disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and nutrition disorders						
Anorexia	25	1	0	14	<1	0
Nervous system disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	10	1	0	7	0	0
Median duration of treatment (d)		**141**			**60**	

Grading according to CTCAE Version 3.0

[a]Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

[b]Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis

(4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).
[c]Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Other notable adverse reactions occurring more frequently with Everolimus than with placebo, but with an incidence of < 10% include:
Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)
General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%), impaired wound healing (< 1%)
Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)
Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasis (4%), skin lesion (4%), acneiform dermatitis (3%)
Metabolism and nutrition disorders: Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (< 1%)
Psychiatric disorders: Insomnia (9%)
Nervous system disorders: Dizziness (7%), paresthesia (5%)
Eye disorders: Eyelid edema (4%), conjunctivitis (2%)
Vascular disorders: Hypertension (4%), deep vein thrombosis (< 1%)
Renal and urinary disorders: Renal failure (3%)
Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)
Musculoskeletal and connective tissue disorders: Jaw pain (3%)
Hematologic disorders: Hemorrhage (3%)

Key laboratory abnormalities are presented in Table
Key Laboratory Abnormalities Reported in Patients with Renal Cell Carcinoma at a Higher Rate in the Everolimus Arm than the Placebo Arm

Laboratory parameter	Everolimus 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[a]						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

Grading according to CTCAE Version 3.0 a Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively pancytopenia), which occurred at lower frequency.

Post-marketing Experience

The following adverse reactions have been identified during post approval use of Everolimus. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure: acute pancreatitis, cholecystitis, cholelithiasis, arterial thrombotic events and reflex sympathetic dystrophy.

OVERDOSAGE

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity was observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

EXPIRY

Please see Manufacturing date and Expiry date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

STORAGE

Store below 25°C. Protect from light and moisture.
Store in the original package and keep out of the reach of children.

PRESENTATION

Strip of 10 tablets supplied in a carton along with Pack Insert.

MARKETED BY

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